

Claims:

1. A method for the diagnosis of one or more single nucleotide polymorphism(s) in flt-1 gene in a human, which method comprises determining the sequence of the nucleic acid of the human at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), and determining the status of the human by reference to polymorphism in the flt-1 gene.
2. A method according to claim 1 in which the single nucleotide polymorphism at position 1953 (according to the position in EMBL accession number X51602) is the presence of G and/or A; and/or at position 3453 (according to the position in EMBL accession number X51602) is the presence of C and/or T; and/or at position 3888 (according to the position in EMBL accession number X51602) is the presence of T and/or C; and/or at position 519 (according to the position in EMBL accession number D64016) is the presence of C and/or T; and/or at position 786 (according to the position in EMBL accession number D64016) is the presence of C and/or T; and/or at position 1422 (according to the position in EMBL accession number D64016) is the presence of C and/or T; and/or at position 1429 (according to the position in EMBL accession number D64016) is the presence of G and/or T; and/or at position 454 (according to the position in SEQ ID No. 3) is the presence of G and/or A; and/or at position 696 (according to the position in SEQ ID No. 5) is the presence of T and/or C.
3. A method as claimed in claim 1 or 2, wherein the nucleic acid region containing the potential single nucleotide polymorphism is amplified by polymerase chain reaction prior to determining the sequence.
4. A method as claimed in any of claims 1 - 3, wherein the presence or absence of the single nucleotide polymorphism is detected by reference to the loss or gain of, optionally engineered, sites recognised by restriction enzymes.

5. A method according to claim 1 or claim 2, in which the sequence is determined by a method selected from ARMS-allele specific amplification, allele specific hybridisation, oligonucleotide ligation assay and restriction fragment length polymorphism (RFLP).

5 6. A method as claimed in any of the preceding claims for use in assessing the predisposition and/or susceptibility of an individual to diseases mediated by an flt-1 ligand.

7. A method for the diagnosis of flt-1 ligand-mediated disease, which method comprises:
i) obtaining sample nucleic acid from an individual;

10 ii) detecting the presence or absence of a variant nucleotide at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene; and,
iii) determining the status of the individual by reference to polymorphism in the flt-1 gene.

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8. An isolated nucleic acid comprising at least 17 consecutive bases of flt-1 gene said nucleic acid comprising one or more of the following polymorphic alleles: A at position 1953 (according to X51602), T at position 3453 (according to X51602), C at position 3888 (according to X51602), T at position 519 (according to D64016), T at position 786 (according to D64016), T at position 1422 (according to D64016), T at position 1429 (according to D64016), A at position 454 (according to SEQ ID No. 3) and C at position 696 (according to SEQ ID No. 5), or a complementary strand thereof.

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9. An allele specific primer or probe capable of detecting an flt-1 gene polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5).

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30 10. A primer as claimed in claim 9 which is an allele specific primer adapted for use in ARMS.

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11. An allele specific nucleotide probe as claimed in claim 9 which comprises the sequence disclosed in any one of SEQ ID Nos: 6 - 14, or a sequence complementary thereto.

12. A diagnostic kit comprising one or more diagnostic primer(s) and/or allele-specific oligonucleotide probes(s) as defined in claims 9, 10 or 11.

13. A method of treating a human in need of treatment with an flt-1 ligand antagonist drug in which the method comprises:

- 10 i) diagnosis of a single nucleotide polymorphism in flt-1 gene in the human, which diagnosis comprises determining the sequence of the nucleic acid at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5);
- 15 ii) determining the status of the human by reference to polymorphism in the flt-1 gene; and
- iii) administering an effective amount of an flt-1 ligand antagonist drug.

14. Use of an flt-1 ligand antagonist drug in the preparation of a medicament for treating a VEGF-mediated disease in a human diagnosed as having a single nucleotide polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene.

15. A pharmaceutical pack comprising an flt-1 ligand antagonist drug and instructions for administration of the drug to humans diagnostically tested for a single nucleotide polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene.

16. An isolated nucleic acid sequence comprising the sequence selected from the group consisting of:

- (i) the nucleotide sequence from positions 1-482 of SEQ ID No. 1;
(ii) the nucleotide sequence from positions 616-1073 of SEQ ID No. 1;
(iii) the nucleotide sequence from positions 1-437 of SEQ ID No. 2;
(iv) the nucleotide sequence from positions 595-1024 of SEQ ID No. 2;
5 (v) the nucleotide sequence from positions 1123-1480 of SEQ ID No. 2;
(vi) the nucleotide sequence from positions 1-266 of SEQ ID No. 3;
(vii) the nucleotide sequence from positions 279-726 of SEQ ID No. 3;
(viii) the nucleotide sequence from positions 1-284 of SEQ ID No. 4;
(ix) the nucleotide sequence from positions 391-651 of SEQ ID No. 4;
10 (x) the nucleotide sequence from positions 795-1352 of SEQ ID No. 4;
(xi) the nucleotide sequence from positions 1-579 of SEQ ID No. 5;
(xii) the nucleotide sequence from positions 665-1256 of SEQ ID No. 5;
(xiii) a nucleotide sequence having at least 80%, preferably at least 90%, sequence identity
to a sequences (i) - (xii);
15 (xiv) an isolated fragment of (i) - (xiii); and
(xv) a nucleotide sequence fully complementary to (i) - (xiv).

17. A computer readable medium having stored thereon a nucleic acid sequence
comprising at least 20 consecutive bases of the flt-1 gene sequence, which sequence includes
20 at least one of the polymorphisms at positions: 1953, 3453, 3888 (each according to the
position in EMBL accession number X51602), 519, 786, 1422, 1429 (each according to the
position in EMBL accession number D64016), 454 (according to SEQ ID No. 3) and 696
(according to SEQ ID No. 5).

- 25 18. A computer readable medium having stored thereon a nucleic acid comprising any of
the intron sequences disclosed in any of SEQ ID Nos. 1 - 5.

19. A method for performing sequence identification, said method comprising the steps of
providing a nucleic acid sequence comprising at least 20 consecutive bases of the flt-1 gene
30 sequence, which sequence includes at least one of the polymorphisms at positions: 1953,
3453, 3888 (each according to the position in EMBL accession number X51602), 519, 786,
1422, 1429 (each according to the position in EMBL accession number D64016), 454

(according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5) in a computer readable medium; and comparing said nucleic acid sequence to at least one other nucleic acid sequence to identify identity.

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.